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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/335,689	06/18/99	TOUSIGNANT J	6969.0028

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LEGAL DEPARTMENT
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EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	19

DATE MAILED: 08/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/335,689	TOUSIGNANT ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2001 and 13 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-15,17-26 and 28-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-15,17-26 and 28-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on 5/4/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/335,689 is acceptable and a CPA has been established. An action on the CPA follows.

Amendments were received on 4/4/01 and 7/13/01 and were entered as Paper Nos. 11 and 18, respectively. Claims 5, 16, and 27 have been canceled, and claims 31-46 have been added as requested. Claims 1-4, 6-15, 17-26, and 28-46 are pending and under consideration in this Office Action.

Claim Objections

Claims 33 and 34 are objected to because of the following informalities: Claims 33 and 34 lack an article at line 5 prior to "micellar complex". Insertion of the word "the" is suggested. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 35-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New claims 35-38 recite the limitation "wherein said method does not necessarily require the formation of a lipid film comprising the cationic lipid." Applicant points to page 16, lines 2-6 to support this limitation. This passage does not refer to, or in any way exclude, the formation of a lipid film. The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See MPEP 2163.05.

-> change to 112/2

what are metes + bounds?

Enablement

Claims 1-4, 6-15, 17-26, and 28-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for micellar complexes and methods of making and using compositions comprising micellar complexes comprising lipid-derivatized PEG, such as are known in the prior art, wherein the size distribution of the all the micellar complexes within a given composition varies by greater than about 20%, does not reasonably provide enablement for methods of making micellar compositions comprising lipid-derivatized PEG, wherein the size

distribution of all the micellar complexes within the composition is less than or equal to about 20%. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claimed inventions encompass methods of making compositions comprising micellar complexes, and methods of using these complexes to deliver biologically active molecules *in vivo*. The complexes comprise at least one cationic lipid, a PEG derivative, and the biologically active substance. The claims require that the size distribution of the micellar complexes cannot vary by more than about 20%. The critical element of the invention is the addition to cationic lipids of a sufficient amount of PEG derivative. Addition of this amount of PEG derivative results in formation of a group of mixed micelles with a narrower size distribution than those observed in at least some prior art formulations. The specification teaches that the amount of PEG derivative which is sufficient varies with "the specific combination of cationic lipid and PEG lipid selected". See page 18, third paragraph. The specification acknowledges that complexes of cationic lipids, biologically active molecules, and lipid-derivatized PEG were known in the prior art. See page 12, lines 4-11. Indeed such compositions are taught by Harris (1998) and Unger (2000). See rejections under 35 USC 102, below. Thus the critical element of the invention, that which allegedly distinguishes it from the prior art, is the addition of "a sufficient amount of PEG derivative".

Guidance as to what constitutes "a sufficient amount of PEG derivative can be found on pages 18, 19, 25, and 38-42. These passages indicate that "the specific combination of cationic lipid and PEG lipid selected" will affect the amount of PEG derivative which is sufficient to produce the desired micellar complexes, and describe three techniques for determining whether or not one has succeeded in adding a sufficient amount of PEG derivative. The specification discloses no example of a sufficient amount of PEG derivative, and provides no guidance as to what quantities of any PEG derivative are sufficient to practice the invention. Neither are any ranges of amounts of PEG derivative suggested. The specification discloses only that the PEG derivative may be added in a certain volume relative to the volume of cationic lipids. See e.g. page 41, first full paragraph. The specification also fails to discuss the principles which govern the effect of PEG derivatives on micelle size, or to otherwise provide any theoretical framework which could be used by one of skill in the art to determine what amount of a PEG derivative, in combination with a cationic lipid, could be used to practice the claimed invention. One might argue that it would not be undue to empirically determine, using the means taught in the specification, the amounts PEG derivative required to practice the claimed invention. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to **known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added.

In this case, the lack of guidance in the specification concerning what constitutes a sufficient amount of PEG derivative is not complemented by teachings in the prior art. Thus the specification fails to teach the most critical element of the invention. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the determination of what constitutes a sufficient amount of PEG derivative cannot be considered a minor detail which can be omitted in the process of providing an enabling disclosure.

Because the specification fails to provide critical elements of the invention, one of skill in the art could not practice the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 6-15, 31, 32, 35, 36, 39, 40, 43, and 44 are indefinite because it is unclear what is intended by the phrase "a sufficient amount of PEG derivative to form micellar lipids". More particularly it is unclear what is intended by the term "micellar lipids". It appears that Applicant may intend to refer to micelles rather than micellar lipids. If Applicant intends to refer to the formation of micelles, then it is suggested that "micelles" should be substituted for the words "micellar lipids". Alternatively, and in agreement with the specification at e.g. page 11, lines 3 and 4, the words "mixed micelle" could be substituted for "micellar lipids". As written, the claim could be construed as requiring the synthesis, by addition of a PEG derivative to a lipid mixture, of lipids capable of forming micelles. Because lipids in general are capable of forming micelles, the addition of PEG derivatives to lipids does not imbue them with this property. Rather, the invention relates to the affect of PEG derivatives on the size distribution of complexes

of biologically active molecules and mixed micelles comprising lipids and PEG derivatives. For this reason it is suggested that the words "mixed micelles" should be substituted for "micellar lipids". This amendment would overcome the rejection of claims 1-4 and 6-15 and more clearly reflect the invention as disclosed by the specification.

Claims 1-4, 6-15, 17-26, and 28-30 are indefinite because they require a variation in size distribution of less than or equal to about 20%, but they fail to provide any standard from which to calculate 20% variation. In other words it is unclear of what quantity 20% is a fraction.

Claims 1-4, 6-15, 17-26, 28-34 are indefinite because they recite "the size distribution" without antecedent basis. The prior art teaches that the size distribution of a given micelle population varies with environmental characteristics such as salt concentration and temperature. For example, Govender et al (J. Contr. Rel. 75(3): 249-258, 2001) teach that PEG-containing micelles can aggregate as salt concentration increases, thus one would expect size distribution of PEG-containing micelles to decrease with increasing salt concentration. Robson et al (Biochim Biophys Acta 573:488-500, 1979) teach that mixed micelles displayed a relatively narrow size distribution at 40° C than at 20° C. See abstract, and compare figures 2C and 3C on pages 192 and 495. Because the claim does not set forth the conditions under which size distribution should be measured, one of skill in the art cannot know the metes and bounds of the claims.

Claims 33 and 34 are indefinite because it is unclear what constitutes "a sufficient amount of a PEG derivative". For what purpose or characteristic must the PEG be sufficient?

Claims 41 and 42 are indefinite because it is unclear what is intended by the limitation "preferably". It is unclear how "preferably" is intended to affect the metes and bounds of the invention. Deletion of the word "preferably" is recommended.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 9-11, 13, 14, 17-19, 21, 22, 24-29, and 31-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Harris et al (US Patent 5,719,131, issued 2/17/98).

Harris teaches methods of making micellar compounds comprising a cationic lipid, a PEG derivatized colipid, and DNA. See column 26, lines 4-11 and 32-36; column 37, lines 24-53; and column 45, line 56 to column 46, line 5.

Claims 9-11, 13, and 14 are product by process claims directed to individual micellar complexes. For the purpose of examination under 35 USC 102, a micellar complex of the invention is considered to be a particle comprising a cationic lipid, a PEG derivative, and a

biologically active molecule such as DNA. There is no evidence of record indicating that the individual complexes of Harris differ from those of the instant invention in any way.

The targeting agent of claim 11 is anticipated because the compositions of Harris may comprise more than one cationic lipid. See column 7, lines 63-65. Cationic lipids can be considered to be targeting agents for mammalian cells.

Claims 13 and 21 are included in this rejection because the method by which Harris makes micellar compositions should inherently result in the formation of complexes comprising lipids coating the DNA of the micellar complexes. Because of the charge interaction between the DNA and the cationic lipids, any lipid which was not incorporated into micelles would be expected to interact with DNA. Furthermore, the micelles themselves could be expected to coat the DNA as well.

The methods of claims 17-19, 21, 22, 24-26, 28, 29, and 39-42 are anticipated because Harris teaches the delivery of DNA to human airway epithelial cells. See Examples 2 and 3, columns 39-42. It is noted that claims 17-19, 21, 22, and 24-29 require a micellar complex which is part of a group having a variation in size distribution less than or equal to 20%. Applicant argued at page 7 of Paper No. 11 that Harris does not teach a micellar complex having a variation in size distribution less than or equal to 20%. However, the claim does not require that all of the complexes in the composition must be a member of that group, and the claim does not set any limit on how many members a group must have. All compositions of micellar complexes must comprise groups of complexes with a size distribution that varies by less than 20%, because

all compositions comprise groups of complexes which have only a single member, and which therefore have no variation in size distribution. Claims 25, 26, 28, and 29 are drawn to a single micellar complex wherein the variation in size distribution of a group of such complexes is less than 20%. These claims read on a micellar complex which, when placed in a group with *identical* micellar complexes, would yield a variation in size distribution of less than 20%. Thus these claims are anticipated by any micellar complex comprising at least one cationic lipid, at least one PEG derivative, and at least one biologically active molecule, because the size distribution of a group of identical complexes is necessarily zero.

Claims 31-34 require a sufficient amount of PEG derivative to form micellar complexes, and require complexes with a size distribution which is narrower than the size distribution of complexes prepared without a sufficient amount of the PEG derivative. However, because lipids can form micelles in the absence of derivatized PEG, any amount of PEG-derivatized lipid used in a micellar complex, or a method of making one, is deemed adequate to anticipate the claims.

Claims 35-38 require a method of making complexes which does not necessarily require the formation of a lipid film comprising the cationic lipid. These claims are anticipated because Harris teaches no such requirement.

Thus Harris anticipates the claims.

Claims 9-14, 17-19, and 21-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Unger (US Patent 6,028,066, filed 5/2/97).

Unger teaches a method of making micellar complexes by combining micellar lipids with a bioactive agent which may be DNA. See column 79, lines 20-37; column 2, lines 59-65; column 6, lines 10-24, especially lines 22 and 23; and column 6, lines 55-57. The micellar lipids may comprise PEG-modified lipids. See column 22, line 19 to column 24, line 1, especially column 22, lines 60-67. The complexes may comprise targeting moieties, and may include peptides with RGD sequences. See column 6, lines 45-51; and column 19, lines 54-58. Unger also teaches delivery of the complexes to mammalian airway cells. See column 84, lines 24-28. The complexes may be less than 200 nm in size. See column 30, lines 44-48.

Claims 9-14 are product by process claims directed to individual micellar complexes. For the purpose of examination under 35 USC 102, a micellar complex of the invention is considered to be a particle comprising a cationic lipid, a PEG derivative, and a biologically active molecule such as DNA. There is no evidence of record indicating that the individual complexes of Unger differ from those of the instant invention in any way.

Claims 13 and 21 are included in this rejection because the method by which Unger makes micellar compositions should inherently result in the formation of complexes comprising lipids coating the DNA of the micellar complexes. Because of the charge interaction between the DNA and the cationic lipids, any lipid which was not incorporated into micelles would be expected to interact with DNA. Furthermore, the micelles themselves could be expected to coat the DNA as well.

The methods of claims 17-19, 21-29, and 39-42 are anticipated because Unger teaches the delivery of DNA to airway epithelial cells. See column 84, lines 24-28. It is noted that claims 17-19, 21, 22, and 24-29 require a micellar complex which is part of a group having a variation in size distribution less than or equal to 20%. Applicant argued at page 8 of Paper No. 11 that Unger does not teach a micellar complex having a variation in size distribution less than or equal to 20%. However, the claim does not require that all of the complexes in the composition must be a member of that group, and the claim does not set any limit on how many members a group must have. All compositions of micellar complexes must comprise groups of complexes with a size distribution that varies by less than 20%, because all compositions comprise groups of complexes which have only a single member, and which therefore have no variation in size distribution. Claims 25, 26, 28, and 29 are drawn to a single micellar complex wherein the variation in size distribution of a group of such complexes is less than 20%. These claims read on a micellar complex which, when placed in a group with *identical* micellar complexes, would yield a variation in size distribution of less than 20%. Thus these claims are anticipated by any micellar complex comprising at least one cationic lipid, at least one PEG derivative, and at least one biologically active molecule, because the size distribution of a group of identical complexes is necessarily zero.

Claims 31-34 require a sufficient amount of PEG derivative to form micellar complexes, and require complexes with a size distribution which is narrower than the size distribution of complexes prepared without a sufficient amount of the PEG derivative. However, because lipids

can form micelles in the absence of derivatized PEG, any amount of PEG-derivatized lipid used in a micellar complex, or a method of making one, is deemed adequate to anticipate the claims.

Claims 35-38 require a method of making complexes which does not necessarily require the formation of a lipid film comprising the cationic lipid. These claims are anticipated because Unger teaches no such requirement.

Thus Unger anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9, 14, 15, 17, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al (US Patent 5,719,131, issued 2/17/98).

Harris teaches methods of making micellar compounds comprising a cationic lipid, a PEG derivatized colipid, and DNA. See column 26, lines 4-11 and 32-36; column 37, lines 24-53; and column 45, line 56 to column 46, line 5. More particularly Harris teaches a method of making micellar complexes wherein 64 different cationic lipid suspensions were combined with equal volumes of 64 different DNA solutions. See column 37, lines 38-52. Briefly, eight 165 microliter lipid suspensions of different concentrations were deposited into eight different wells of a

microtiter plate. Sixty-four different lipid suspensions were then made by seven 2-fold dilutions of the initial eight suspensions. This results in 64 suspensions of 165 microliters each. A similar operation was carried out for the DNA solutions, and the contents of the two microtiter plates were combined pair-wise resulting in 64 lipid/DNA suspensions. Among the mass ratios of lipid to DNA encompassed were ratios of 0.7:1; 1.4:1; 5.6:1, and 11.2:1 (w/w).

Harris does not teach the combination of lipid and DNA in an 8:1 (vol/vol) ratio. However, this volume ratio would have been obvious in view of the fact that Harris could just as easily have used equimolar solutions of both lipids and DNA, and added the appropriate volumes of each to arrive at the range of mass ratios disclosed. One would have been motivated in this instance to use a ratio of 8:1 (vol/vol) to achieve a lipid :DNA mass ratio of 8:1. One would have been motivated to obtain this ratio because the ratio of concentrations of lipid and DNA in these complexes is a result-effective variable. That is, the results of a technique using the compositions are effected by concentrations of each of these variables, and one of ordinary skill would be motivated to optimize the concentrations of each variable. Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that this concentration is critical. See MPEP 2144.05(b). In this case, the specification discloses that ratios of 1:1 and 8:1 are operable. See Figs. 3 and 4. Thus the ratio of 8:1 is not required for the function of the invention. As noted above, Harris teaches ratios covering the range of ratios disclosed as operable by Applicant. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable

ranges by routine experimentation." *In re Aller*, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955). Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 103-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Patsy Zimmerman whose telephone number is 703-308-8338.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.